to a section of the skin of a patient exhibiting fine lines, clinical wrinkles or non-precancerous, normal photodamage photo-damage, wherein the patient is not being treated for viral infection or skin cancer at the same section of the skin.

Remarks

Claims 11, 12, 14, and 19 – 21 stand rejected under 35 U.S.C. § 112, Second Paragraph. These claims have been amended in a manner that Applicants respectfully submit overcome these rejections.

Claims 11, 13, 14, 19 – 21, 27 and 28 stand rejected under 35 U.S.C. § 102(b) as anticipated by Stockfleth *et al.*, "Successful treatment of actinic keratosis with imiquimod cream 5%: a report of six cases," *Br. J. Dermatol.*, Vol. 144, pp. 1050 – 1053 (2001). Claims 12, 15 – 18 and 29 stand rejected under 35 U.S.C. § 103(a) as obvious based on the teachings of Stockfleth. Claims 11-21 stand rejected as obvious based on the teachings of US Patent Application Publication No. 2003/0072724 to Maibach *et al.* For the reasons set out below, including those set forth in the Expert Affidavit of Neil Swanson M.D., submitted under 35 U.S.C. § 1.132, Applicants respectfully traverse the rejections under 35 U.S.C. §§ 102(b) and 103(a) because neither Stockfleth nor Maibach teach or suggest all of the claim limitations, as amended.

Applicants thus respectfully request entry of the amendments to the claims and timely notice of allowance.

A. **35 U.S.C. § 112**

Claims 11, 12, 14, and 19 – 21 stand rejected under 35 U.S.C. § 112, Second Paragraph. These claims have been amended to describe the claimed imidazoquinoline amine derivatives as conforming to a specific structural formula. Support for this amendment is found in US Patent No. 4,689,338 which is incorporated by reference in its entirety in Paragraph [0019] of the Application. More particularly, when R_1 is isobutyl,

and each R_2 group and R_3 are hydrogen, imidazoquinoline amine derivative is imiquimod, which is specifically claimed as 1-isobutyl-1H-imidazo [4,5-c] quinolin-4-amine in claims 13 and 15 – 18.

A minor modification to the description of imidazoquinoline amine derivative is made in claims 13 and 15 – 18 to conform to established principles of chemical nomenclature. More particularly, a comma was deleted after the number 5 and the letter c is now in lowercase form.

The imidazoquinoline amine derivatives claimed in newly-added Claims 30 – 32 are likewise disclosed in the US Patent No. 4,689,338.

Claim 11 is further amended to clarify the nature of the photodamage as being non-precancerous, normal photo-damage. Support for this clarification is found in Paragraph [0021] of the Application.

Claim 11 is also amended to add fine lines as a skin condition that may be treated according to the methods claimed in the present invention. Support for this amendment is found throughout the Application including Paragraph [0008].

The imidazoquinoline amine derivatives claimed in newly-added Claim 33 are taught in Izumi *et al.*, "1H-Imidazo [4,5-c] quinoline derivatives as novel potent TNF-alpha suppressors: synthesis and structure-activity relationship of 1-, 2- and 4-substituted 1H-imidazo [4,5-c] quinolines or 1H-imidazo [4,5-c] pyridines," *Bioorg. Med. Chem.* Vol. 11, No. 12, pp. 2541-50 (2003). *See*, in particular, Table 1 at page 2543. The disclosure of the Izumi article is incorporated by reference in its entirety in Paragraph [0019] of the Application

The imidazoquinoline amine derivatives claimed in newly-added Claim 34 are taught in van Galen *et al.*, "1H-imidazo [4,5-c] quinolin-4-amines: novel non-xanthine adenosine antagonists," *J. Med. Chem.* Vol. 34, No. 3, pp. 1202-6 (1991). *See*, in

particular, Table 1 at page 1204. The disclosure of the van Galen article is incorporated by reference in its entirety in Paragraph [0019] of the Application

Copies of the Izumi and van Galen articles were previously submitted in the Information Disclosure Statement dated December 17, 2003.

New matter is not added by the above amendments.

B. 35 U.S.C. § 102(b)

Claims 11, 13, 14,19 – 21,27, and 28, are rejected under 35 U.S.C. 102(b) as being anticipated by Stockfleth et al. which teaches the topical treatment of actinic keratoses (AKs) with a cream containing imiquimod, one of the imidazoquinoline amine derivatives claimed in the present application, at a concentration of 5%. For the following reasons, Applicants respectfully traverse.

AKs are precancerous lesions. *See*, Section 1.132 Affidavit of Dr. Neil Swanson, ¶ 7. The present invention does not relate to the treatment of precancerous skin conditions. Instead, a person of skill in the art would understand that one aspect of the present invention relates to treating intrinsically-aged skin (*i.e.*, skin containing fine lines or wrinkles). Another aspect of the present invention relates to the treatment of normal photodamaged skin, which is defined in Paragraph [0021] of the Application to mean "non-precancerous skin." *See* Swanson Affidavit, ¶ 12.

Normal (*i.e.*, non-precancerous) photodamaged skin and aged skin differ considerably from AKs, both in clinical and histological presentation. *See* Swanson Affidavit, ¶¶ 8 - 11.

Moreover, as set forth in Paragraph 13 of the Swanson Affidavit, Stockfleth does not teach or suggest to a person of ordinary skill in the art the use of imiquimod in either intrinsically-aged skin or normal, photodamaged skin.

Additionally, Stockfleth cautions that the use of imiquimod at a 5% concentration in the treatment of precancerous skin conditions was found to be irritating. As Dr. Swanson explains, such an adverse effect would have cosmetic dermatologist away from treating non-cancerous or non-viral skin conditions in the manner claimed in the present application. *See* Swanson Affidavit, ¶ 14.

C. 35 U.S.C. § 103(a)

Claims 12, 15 – 18 and 29 stand rejected under 35 U.S.C. § 103(a) as obvious based on the teachings of Stockfleth. Claims 11-21 also stand rejected as obvious under 35 USC based on the teachings of US Patent Application Publication No. 2003/0072724 to Maibach *et al.* For the following reasons, Applicants respectfully traverse.

As a preliminary matter, Applicants respectfully note that the Office Action does not make out a *prima facie* case of obviousness under the four-part test articulated by the Supreme Court in *Graham v. John Deere*, 383 U.S. 1, 148 USPQ 459 (1966). The third factor in a Graham inquiry is to resolve the level of ordinary skill in the pertinent art. The Office Action fails to do so.

Applicants respectfully submit that in the case of the present invention, the person of ordinary skill in the art is a board certified dermatologist.

With respect to the obviousness rejections based on Stockfleth, Applicants respectfully traverse. As explained in Paragraph 13 of the Swanson Affidavit, Stockfleth does not teach or suggest to a person of ordinary skill in the art to use imiquimod in treating either intrinsically-aged skin or normal, photodamaged skin. Instead, Stockfleth teaches the use of imiquimod at a concentration reported to be irritating (5%) to treat precancerous lesions.

Applicants respectfully traverse the obviousness rejections based on Maibach *et al.* The present application is not directed to the use of imiquimod to treat viral infections. Indeed, Claim 11 recites a negative limitation, disclaiming the use of the claimed imidazoquinoline amine derivatives on aged or normal photodamaged skin that is otherwise being treated for viral infection.

As Dr. Swanson explains in Paragraph 15 of his Section 1.132 Affidavit, the sole reference to imiquimod in the Maibach *et al.* patent application is with respect to the treatment of warts which are well-known to persons of skill in the art to be caused by the papilloma virus. Rather the teachings of the Maibach application are directed to the use of known depigmenting active ingredients – hydroquinone, kojic acid, glycolic acid and other alpha-hydroxy acids, and artocarpin – for the treatment of hyperpigmentation in a specific dermopharmaceutical base containing specific permeation enhancers. Treating hyperpigmentation would not be understood by persons of skill in the art as treating fine lines and wrinkles.

The novelty and non-obviousness of the claimed invention – *e.g.*, the use of imiquimod and other imidazoquinoline amine derivatives to treat fine lines and wrinkles in aged skin and/or normal, non-precancerous photodamaged skin – is further illustrated by a 2005 review article by Drs. Vender and Goldberg (copy attached to the Swanson Affidavit) entitled "Innovative Uses of Imiquimod", which reports on the successful treatment of over forty dermatologic conditions, anecdotally or in clinical trial settings. *Journal of Drugs in Dermatology*, Vol. 4, No. 1, pp. 58 – 63. As discussed in Paragraph 17 of the Swanson Affidavit, the Vender article is an extensive review of clinical trials, case reports and letters published in peer-reviewed journals regarding imiquimod use in treating skin disorders. It is based on searches of five medical/scientific databases – MEDLINE, EMBASE, Biosis, SciSearch and International Pharmaceutical Abstracts.

Treatment of normal photodamaged skin (i.e., non-precancerous skin) is not mentioned. Nor is treatment of fine lines and wrinkles in aged skin.

A 2006 article in the Dermatology Times (copy attached to the Swanson Affidavit) further attests to the surprising and unexpected nature of the invention claimed in the present application. The article quotes Albert Kligman, M.D., Ph.D., Professor Emeritus in the Department of Dermatology at the University of Pennsylvania School of Medicine. According to Dr. Kligman, topical use of imiquimod to treat fine lines and wrinkles surprisingly did not cause local adverse reactions, as had been reported by Stockfleth *et al.* *See*, Swanson Affidavit, ¶ 18.

Conclusion

For the above reasons, reexamination, reconsideration and allowance of all the claims as amended are respectfully requested. If the Examiner believes that an interview will expedite allowance, please contact undersigned counsel.

Respectfully submitted,
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